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Discovery of *N*-Hydroxy-2-(2-oxo-3-pyrrolidinyl)acetamides as Potent and Selective Inhibitors of Tumor Necrosis Factor-α Converting Enzyme (TACE)

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Abstract—New inhibitors of tumor necrosis factor-α converting enzyme (TACE) were discovered using an *N*-hydroxy-2-(2-oxo-3-pyrrolidinyl)acetamide scaffold. The series was found to be potent in a porcine TACE (pTACE) assay with IC_{50}s typically below 5 nM. For most compounds, selectivity for pTACE relative to MMP-1,-2, and -9 is at least 300-fold. Compound **2o** was potent in inhibition of TNFα production in a human whole blood assay (WBA) with an IC_{50} of 0.42 μM.

Tumor necrosis factor-α (TNFα), produced primarily by activated macrophages and T-cells, is a cytokine with well-established pro-inflammatory properties.[1] Anti-TNFα proteins (antibodies and receptor fusion proteins) have demonstrated remarkable efficacy clinically in patients suffering from rheumatoid arthritis, Crohn's disease, and psoriasis.[2] Consequently, there has been strong interest in discovering small molecule drugs that selectively suppress TNFα activity.[3] TNFα is expressed as a membrane-associated 26 kDa form (pro-TNFα) from which a soluble 17 kDa form is produced by a metalloprotease named TNFα converting enzyme (TACE).[4] The homotrimer of soluble TNFα binds to TNF receptor (TNFR) to induce trimerization of the receptor, which triggers signaling pathways leading to cell activation. In spite of many attempts, a chemically tractable small molecule which inhibits TNFα-TNFR binding has remained elusive.[5] An alternative approach is to suppress the production of TNFα by inhibition of TACE.

TACE (ADAM-17) belongs to a subclass of metzincins that has a disintegrin and a metalloprotease domain. A related class of metzincins, matrix metalloproteinases (MMPs), has attracted considerable interest in drug discovery because of their pathological roles in arthritic and oncological diseases. A subset of MMP inhibitors was found to inhibit TACE and thus served as early leads for the TACE research.[6] Because most broad-spectrum MMP inhibitors have been reported to cause musculoskeletal side effects in clinical trials,[7] it is desirable to develop TACE inhibitors devoid of MMP activity.[8,9]

Recently, we reported a series of TACE inhibitors derived from a novel *N*-hydroxy-2-(2-oxo-1-pyrrolidinyl)acetamides (lactam **1**, Fig. 1).[8a] The lactam scaffold was designed by taking advantage of the structure of MMP-3 and the apparent similarity between the active site regions of TACE and MMP-3, revealed from early TACE inhibitors. A computer model of a lactam analogue **1b** in MMP-3 suggested that the hydroxamate group binds to the catalytic zinc ion in a bidentate fashion and the carbonyl group of the γ-lactam forms two important hydrogen bonds with the NH groups of Val163 and Leu164 (Fig. 2). A structure–activity relationship (SAR) study indicated that the lactam scaffold binds to TACE in a similar mold.[8a] Optimization of **1a** led to the discovery of [(2-methyl-4-quinolinyl)methoxy]-phenyl P1′ group as the critical determinant of selectivity for TACE relative to MMPs. To broaden the TACE inhibitor portfolio, we examined in silico the feasibility of flipping the γ-lactam ring of **1** and found that the *N*-

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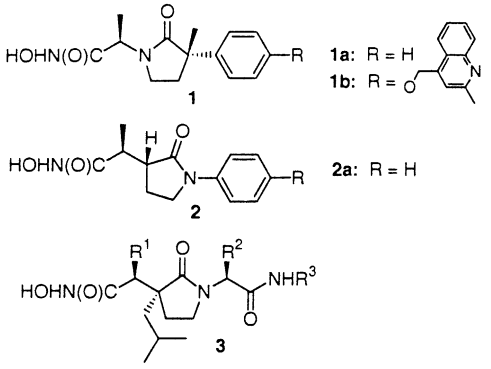


Figure 1. Representative lactam inhibitors of TACE (**1** and **2**) and MMPs (**3**).

hydroxy-2-(2-oxo-3-pyrrolidinyl)acetamide scaffold (lactam **2**) can be modeled in the active site of MMP-3. As shown in Figure 2, an analogue of the new lactam, **2a**, is nicely supposed with **1a**. This paper discloses the synthesis and evaluation of this new γ-lactam series. A related lactam, **3**, has been reported as MMP inhibitors.[10] However, lactam **2** is distinctive from **3** in that the [(2-methyl-4-quinolinyl)methoxy]phenyl P1′ group in **2** is attached to the nitrogen of the lactam ring, whereas lactam **3** was designed to mimic the more traditional binding mode of succinates and requires the opposite configuration at α-position of the lactam to project the isobutyl group to the S1′ site of MMPs.

The synthesis of lactams **2b** and **2c** is outlined in Scheme 1. 4-Pentenoic acid (**4**) was first coupled with Evans (*S*)-4-benzyl-2-oxazolidinone. Stereoselective alkylation of the resulting imide with LDA and *tert*-butyl bromoacetate yielded aldehyde **5** after ozonolysis. Formation of the lactam core was accomplished by reductive amination of **5** with 4-benzyloxyaniline and NaBH(OAc)$_3$ and subsequent cyclization in toluene at elevated temperature. In an attempt to induce stereoselective methylation, the oxazolidinone chiral auxiliary was installed to **6**. Unfortunately, the methylation reaction proceeded in 2:1 selectivity in favor of the undesired (*R*)-methyl isomer. Removal of the benzyl protecting group in **7** was followed by alkylation using 4-chloromethyl-2-methylquinoline and Cs_2CO_3 in DMSO. Finally, the oxazolidinone chiral auxiliary was displaced with NH_2OH in the presence of KOH to complete the synthesis of **2b** and **2c**, which were separated by reverse phase HPLC. Lactam **2d** was also synthesized using this route.

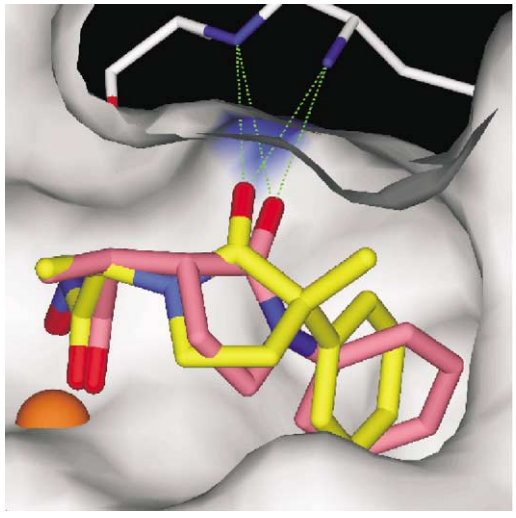
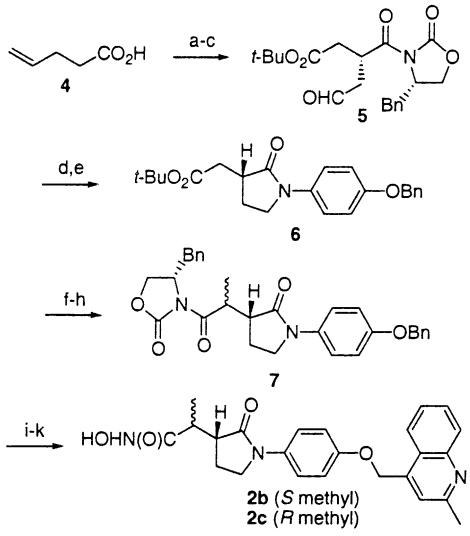


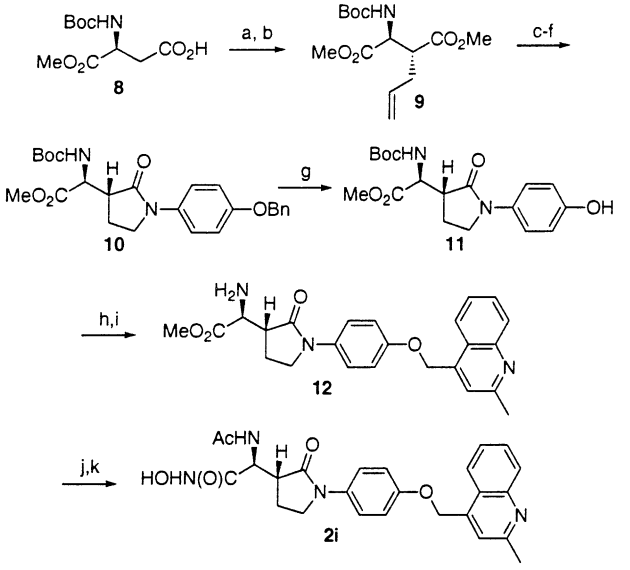
Figure 2. Model of lactams **1a** and **2a** in MMP-3. Nitrogen atoms are blue, oxygens red, carbon atoms of **1a** yellow and those of **2a** pink. Residues of the MMP-3 in the backbone of the strand just above the active site (Val163-Leu164) are white. Other amino acids are omitted for clarity.

Synthesis of lactams with an amino substituent at the α-position of the hydroxamate is outlined in Scheme 2. Aspartic acid **8** was first esterified with MeI and DBU. The resultant ester was deprotonated with LiHMDS and reacted with allyl bromide to afford the desired *anti* product **9** in 15:1 ratio. After ozonolysis, the aldehyde was reacted with 4-benzyloxyaniline to form a Schiff base, reduced to amine with NaBH(OAc)$_3$ and cyclized in toluene at reflux to provide lactam **10**. The (2-methyl-4-quinolinyl)methyl P1′ group was incorporated using a two-step sequence to give amine **12** after hydrolysis of the Boc protecting group. Acetylation and hydroxamic acid formation completed the synthesis of **2i**. Lactams **2f–h** and **2j–o** were synthesized from common intermediate **12**. Preparation of lactam **2e** followed the same sequence but using dimethyl malate in place of aspartic acid **8**.

A series of analogues with an amino substituent at the α-position of the lactam (**2p–t**) were prepared in racemic form using the route shown in Scheme 3. Aspartic acid **8** was treated with 2 equivalents of LDA and reacted with allyl bromide to construct the quaternary center. Ester-



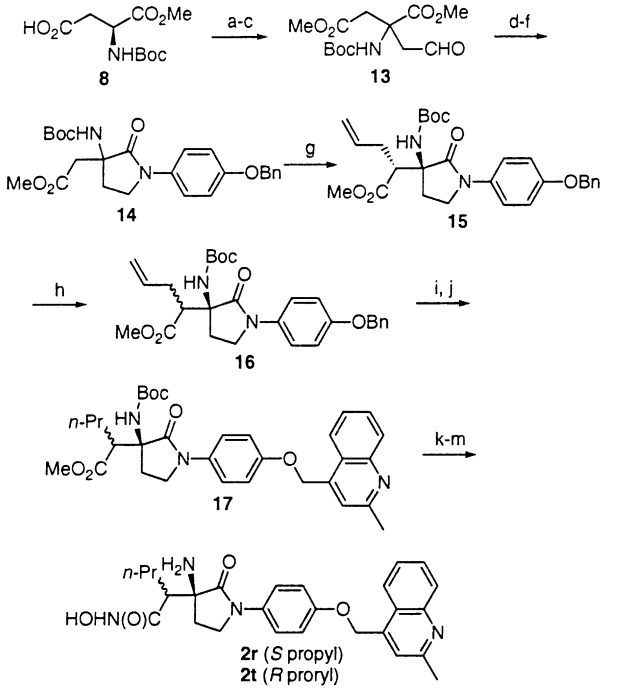
Scheme 1. Reagents and conditions: (a) PivCl, Et_3N, BuLi/(*S*)-4-benzyl-2-oxazolidinone, THF (86%); (b) LDA, $BrCH_2CO_2$-*t*-Bu, THF (64%); (c) O_3, CH_2Cl_2, PPh_3 (87%); (d) 4-benzyloxyaniline, NaBH(OAc)$_3$, $ClCH_2CH_2Cl$; (e) toluene, at reflux (60% for two steps); (f) CF_3CO_2H, CH_2Cl_2 (100%); (g) PivCl, Et_3N, BuLi/(*S*)-4-benzyl-2-oxazolidinone, THF (83%); (h) KHMDS, MeI, THF (42%, α/β = 2:1); (i) H_2, $Pd(OH)_2$/C, MeOH (74%); (j) 4-chloromethyl-2-methylquinoline, Cs_2CO_3, DMSO (77%); (k) NH_2OH, KOH, MeOH (51%).



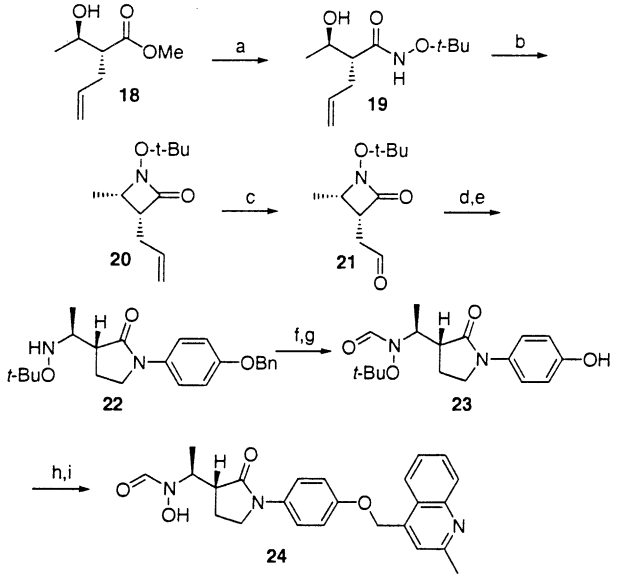
Scheme 2. Reagents and conditions: (a) MeI, DBU, toluene, at reflux (96%); (b) allyl bromide, LiHMDS, toluene, THF (61%, 15:1 ratio of *anti*/*syn* isomers); (c) O_3, CH_2Cl_2, PPh_3 (71%); (d) 4-benzyloxyaniline, toluene, at reflux; (e) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (f) toluene, at reflux (46% for 3 steps); (g) H_2, $Pd(OH)_2/C$, MeOH (74%); (h) 4-chloromethyl-2-methylquinoline, Cs_2CO_3, DMSO (86%); (i) CF_3CO_2H, CH_2Cl_2 (quantitative); (j) Ac_2O, *i*-Pr_2NEt, CH_2Cl_2 (87%); (k) NH_2OH, KOH, MeOH (51%).

ification and ozonolysis provided aldehyde **13**, which was converted to lactam **14** using the three-step sequence described previously. When **14** was treated with LDA and allyl bromide, a single allylation product with (*R*)-allyl configuration (**15**) was isolated in 36% yield. Deprotonation of this allyl product with LDA and quenching with MeOH afforded **16** as a 1:3 mixture of (*S*)- and (*R*)-allyl isomers. The mixture was not separated but subjected to catalytic hydrogenation conditions to reduce the double bond and remove the benzyl group to give **17**, after alkylation with 4-chloromethyl-2-methylquinoline. The Boc group was hydrolyzed and the ester saponified to give the desired acid mixture, which were separated by reverse phase HPLC. Each diastereomer was coupled with hydroxylamine using BOP reagent to complete the synthesis of **2r** and **2t**.

An *N*-hydroxyformamide analogue of the lactam (**24**) was synthesized using reactions depicted in Scheme 4. β-Hydroxy ester **18**, a known compound prepared using Frater alkylation,[11] was reacted with *tert*-butoxyamine under Weinreb's trimethylalluminium conditions. The reaction was clean but sluggish even at reflux and the low yield of hydroxamate product **19** (47%) was due to incomplete reaction. Hydroxamate **19** was cyclized under Mitsunobu conditions to afford β-lactam **20**, which was converted to aldehyde **21** via ozonolysis. Coupling of **21** with 4-benzyloxyaniline using $NaBH(OAc)_3$ as a reducing agent yielded a secondary amine. Heating the amine in toluene at reflux effected translactamization to provide the more stable γ-lactam **22**. The *tert*-butoxyamino group was then formylated using acetyl formyl mixed anhydride[12] in pyridine at elevated temperature. Phenol **23**, obtained after



Scheme 3. Reagents and conditions: (a) LDA, allyl bromide, THF; (b) MeI, K_2CO_3, DMF (65% for two steps); (c) O_3, CH_2Cl_2, PMe_3 (85%); (d) 4-benzyloxyaniline, toluene, at reflux; (e) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (f) toluene, at reflux (41% for three steps); (g) LDA, allyl bromide, THF (36%); (h) LDA, THF, MeOH (90%); (i) H_2, Pd/C, MeOH (100%); (j) 4-chloromethyl-2-methylquinoline, Cs_2CO_3, TBAI, DMSO (61%); (k) HCl, dioxane (100%); (l) KOH, MeOH (41%); (m) NH_2OH, BOP, *i*-Pr_2NEt, DMF (40%).



Scheme 4. Reagents and conditions: (a) *t*-$BuONH_2$, Me_3Al, CH_2Cl_2, THF, at reflux (47%); (b) DEAD, PPh_3, THF (67%); (c) O_3, CH_2Cl_2, PPh_3 (81%); (d) 4-benzyloxyaniline, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (e) toluene, at reflux (62% for two steps); (f) AcOCHO, pyridine, at reflux (53%); (g) H_2, $Pd(OH)_2/C$, MeOH (quantitative); (h) 4-chloromethyl-2-methylquinoline, Cs_2CO_3, DMSO (90%); (i) CF_3CO_2H, CH_2Cl_2 (quantitative).

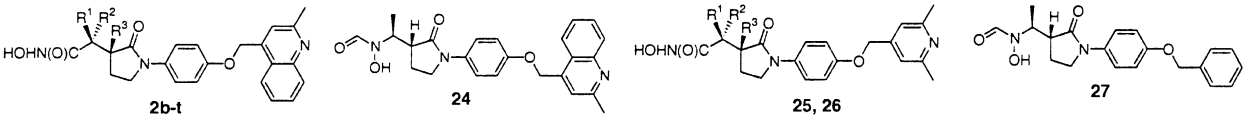
debenzylation, was alkylated with 4-chloromethyl-2-methylquinoline. The *tert*-butyl protecting group was then removed with CF_3CO_2H to complete the synthesis of **24**.

Semi-purified porcine TACE (pTACE) from porcine spleen was used in the primary assay.[13,14] Selectivity profile was evaluated using MMP-2 and -9 as representative members with deep S1′ pocket and MMP-1 as a representative with shallow S1′.[13,14] Cellular activity was assessed using LPS-stimulated human whole blood assay (WBA) where inhibition of TNFα production was measured.[13]

Because the (2-methyl-4-quinolinyl)methoxy P1′ group has been optimized for potency and selectivity in the *N*-hydroxy-2-(2-oxo-1-pyrrolidinyl)acetamide series (lactam **1**, Fig. 1),[8a] this group was kept constant in most of the structure–activity relationship (SAR) study discussed in this paper. We were delighted to find that compound **2b** ($R^1 = Me$, $R^2 = R^3 = H$, Table 1) was extremely potent in the pTACE assay with an IC_{50} of 1 nM. Lactam **2b** also exhibited excellent selectivity (at least 1200-fold) relative to MMP-1, -2, and -9. Inversion of the stereocenter at α-position of the hydroxamate group resulted in 50-fold loss of pTACE potency (**2c**, $R^2 = Me$, $R^1 = R^3 = H$). Similarly, the propyl analogue with inverted configuration (**2d**) is not potent, either. These data are consistent with the proposed binding conformation and lent validation to the prediction that lactam **2** mimics the binding of **1** (Fig. 2). In the proposed conformation, R^2 group, when other than a hydrogen, clashes with the backbone of the protein, whereas R^1 group points toward solvent and hence is expected to tolerate variations.

Despite its affinity for pTACE, lactam **2b** is only moderately effective in inhibiting TNFα production in human whole blood assay ($IC_{50} = 1.57$ μM, Table 1). Activity in WBA is complicated by multiple factors and the foremost of which are protein binding and cell membrane permeability (most of pro-TNFα processing occurs intracellularly[15]). Because the R^1 group was predicted to be exposed to solvent and have minimal contact with the protein (Fig. 2), we tried to modulate the WBA potency using different R^1 group. The hydroxy and amino groups (**2e**,**f**) had essentially no effect on the IC_{50} value of pTACE or WBA (Table 1) as compared to **2b**. The dimethylamino compound **2g** was 7-fold less active for pTACE compared to **2b**. However, **2g** remained as potent as **2b** in the WBA, which could be in part attributed to the relatively high free fraction in human serum (31% unbound). Pyrroly substitution (**2h**) attenuated pTACE activity. Acetylamino compound **2i** gave comparable potency in pTACE and WBA to **2b**, but had diminished selectivity over MMP-2. Benzamide and *n*-butyl carbamate analogues **2j** and **2k** were less potent in the cell assay. Compounds **2l–n** were highly potent in pTACE assay ($IC_{50} < 1$ nM). Notably, the morpholinyl carbamate **2m** resulted in the first sub-micromolar inhibitor in the WBA (0.84 μM) for the series, a 2-fold improvement over **2b**. Unfortunately, the WBA activity of **2l** and **2n** did not track with their pTACE affinity. The Boc-protected amino analogue **2o** is potent in the WBA with an IC_{50} of 0.42 μM. Even though it picked up moderate MMP activity, **2o** is still 700-fold selective over MMP-1 and

Table 1. In vitro potency of lactams **2a–s** and **24–27** in pTACE, MMP-1, -2, and -9, and WBA



Compd	R^1	R^2	R^3	pTACE IC_{50}, nM[a]	MMP-1 K_i, nM[a]	MMP-2 K_i, nM[a]	MMP-9 K_i, nM[a]	WBA IC_{50}, μM[b]
2b	Me	H	H	1	> 5000	1267	> 2000	1.57
2c	H	Me	H	52	> 5000	> 3000	> 2000	> 3
2d	H	*n*-Pr	H	140	> 5000	> 3000	> 2000	—[c]
2e	OH	H	H	3	> 5000	> 3000	> 2000	2.4
2f	NH_2	H	H	2	> 5000	446	1964	1.7
2g	NMe_2	H	H	7	> 5000	> 3000	> 2000	1.5
2h	1-pyrrolyl	H	H	26	> 5000	> 3000	> 2000	> 10
2i	NHAc	H	H	1	> 5000	194	> 2000	1.56
2j	NHC(O)Ph	H	H	1	> 5000	435	> 2000	9.1
2k	$NHCO_2$-*n*-Bu	H	H	2	1627	305	> 2000	6.83
2l	NHPiv	H	H	< 1	> 5000	1244	> 2000	4.95
2m	NHC(O)-4-morpholinyl	H	H	< 1	> 5000	805	> 2000	0.84
2n	$NHCO_2Me$	H	H	< 1	> 5000	482	> 2000	2.65
2o	NHBoc	H	H	1	788	324	291	0.42
2p[d]	H	H	NH_2	5	> 5000	> 3000	> 2000	4.8
2q[d]	Me	H	NH_2	2	> 5000	> 3000	> 2000	1.1
2r[d]	*n*-Pr	H	NH_2	4	> 5000	> 3000	> 2000	> 3
2s[d]	Me	H	NMe_2	12	> 5000	433	1299	> 3
2t[d]	H	*n*-Pr	NH_2	405	> 5000	> 3000	> 2000	> 10
24	—	—	—	2	> 5000	> 3000	> 2000	8.7
25	NH_2	H	H	50	> 5000	> 3000	> 2000	> 10
26	NHBoc	H	H	6	2238	> 3000	—[c]	> 3
27	—	—	—	111	> 5000	567	> 2000	> 10

[a]pTACE IC_{50} and MMP K_i values are from a single determination.
[b]Inhibition of TNFα release in WBA was determined with three donors.
[c]Not tested.
[d]Compounds **2p–t** were tested as a racemic mixture.

approximately 300-fold selective over MMP-2 and -9. Lactam **2o** also had good permeability in Caco-2 assay ($P_{app} = 11 \times 10^{-6}$ cm/s), indicating that it may have good oral absorption in vivo. The high affinity obtained with most of the R^1 analogues further validated the computer model shown in Figure 2.

In an attempt to further improve cellular potency, an amino group was introduced to the 3-position of the pyrrolidinone (R^3). Unfunctionalized amino group yielded potent and selective TACE inhibitors (**2p–r**, racemic mixture) regardless whether R^1 is present (methyl and *n*-propyl) or not. Unfortunately, none of them improved WBA potency, with **2q** the most promising at 1.1 μM. Dimethylamino R^3 analogue (**2s**) is 6-fold less potent for pTACE than the amino compound **2q**. Similar to the SAR trend observed with R^3 being hydrogen, inversion of stereocenter at the α-position of the hydroxamate resulted in 100-fold loss of potency (**2t** vs **2r**).

N-Hydroxyformamide (retrohydroxamate) group has been reported to be an effective zinc-binding group to replace the commonly used hydroxamte group in MMP and TACE inhibitors.[9a,16] Hence, *N*-hydroxyformamide analogue **24** was prepared and tested. Indeed, it was highly potent for pTACE (2 nM) and exhibited excellent selectivity relative to the three MMPs (at least 1000-fold). However, it did not offer any advantages over the conventional hydroxamate in the WBA and was approximately 5-fold less potent than **2b**.

Two analogues (**25** and **26**) with (2,6-dimethylpyridinyl)methoxy group in place of the (2-methyl-4-quinolinyl)methoxy P1′ group were evaluated. In both cases, significant loss of enzyme and cell activity was observed (**25** vs **2f**, **26** vs **2o**). For the *N*-hydroxyformamide-derived inhibitor, an analogue with benzyloxy P1′ group (**27**) also had diminished TACE affinity (50-fold) compared to **24**. These data demonstrated that the (2-methyl-4-quinolinyl)methoxy group remained a superior P1′ group for this new series of lactam TACE inhibitors.

In summary, new TACE inhibitors were discovered using an *N*-hydroxy-2-(2-oxo-3-pyrrolidinyl)acetamide scaffold (**2**). Incorporation of the TACE selective (2-methyl-4-quinolinyl)methoxy P1′ group produced a series of highly potent inhibitors of TACE that are selective relative to MMP-1,-2, and -9. Many compounds were also active in the cellular assay (WBA), with **2o** being most potent with an IC_{50} of 0.42 μM. The discovery of this series added diversity to our TACE inhibitor portfolio and can potentially offer new opportunity to develop TACE inhibitors for the treatment of rheumatoid arthritis.

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13. Details of pTACE, MMP-1,-2, and -9 assays and LPS-stimulated human whole blood assay of TNF production are described in ref 7b.

14. The nomenclature for the metalloproteases discussed is as follows: TACE (tumor necrosis factor-α converting enzyme, ADAM-17), MMP-1 (human fibroblast collagenase), MMP-2 (gelatinase-A), and MMP-9 (gelatinase B).

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